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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,653	ORNTOFT ET AL.	
	Examiner	Art Unit	
	SEAN AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68-135* is/are pending in the application.

4a) Of the above claim(s) *91 and 108-135* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68-90 and 92-107* is/are rejected.

7)☒ Claim(s) *74, 104* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restriction

The response filed on 3/25/11 to the restriction requirement of 8/20/10 has been received. Applicant has elected Group I and the following species: the distinct combination of polynucleotides SEQ ID NO:1-135. All unelected species remain withdrawn (see MPEP 803.02).

Claims 68-135 are pending.

Claims 91 and 108-135 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 68-90 and 92-107 are currently under consideration.

Claim Objections

Claim 74 is objected to because of an apparent typographical error. Claim 74 recites: "…wherein at least two of said plurality of gene expression products forming a pattern are used to determine said microsatellite status are selected individually from…". The word "are" before "used" appears out of place. It is noted the following amendment would obviate this objection: "…wherein at least two of said plurality of gene expression products forming a pattern ~~are~~ used to determine said microsatellite status are selected individually from…". Proper correction is required.

Claim 104 is objected to because of an apparent typographical error. Claim 104 appears to misspell the word “consisting”. Replacing “conssiting” with “consisting” would obviate this objection. Proper correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 68-90, 92, and 93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 68 recites the limitation “the tumor”. There is insufficient antecedent basis for “the tumor” in the claim. It is noted that amendments replacing the term “the tumor” with “a tumor” would obviate this rejection. It is further noted the rejections below are based on such amendments.

Claims 75, 82, and 83 recite the limitation "used to determine said hereditary or sporadic nature or colon cancer" in reference to claim 68. There is insufficient antecedent basis for this limitation in the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 68-90, 92, 93, and 97-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods wherein a particular microsatellite status of a colorectal cancer tumor is determined based on higher or lower levels of particular polynucleotides disclosed in Table 17 and methods wherein downregulation of MLH1 polynucleotides in colorectal tumor samples is indicative of patients with sporadic disease and downregulation of PIWIL1 polynucleotides in colorectal tumor samples is indicative of patients with hereditary cases (pages 67-69, in particular), **the specification does not reasonably provide enablement for** methods wherein just any microsatellite status of just any type of tumor from a cancer patient and just any prognostic marker determined from the amount or presence of just any plurality of gene expression products in just any sample from the cancer patient is indicative of just any classification of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to methods wherein just any microsatellite status of just any type of tumor from a cancer patient and just any prognostic marker determined from the amount or presence of just any plurality of gene expression products in just any sample from the cancer patient is indicative of just any classification of cancer. This includes methods wherein gene expression products are either polynucleotides or polypeptides. This includes methods wherein just any type of cancer is classified. This further includes contradictory methods wherein, for example, a tumor with a particular microsatellite status and the presence of a particular prognostic marker is equally indicative of both a good status and a bad status. This further includes methods using expression products of any gene to determine a prognostic marker.

This invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology". Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The specification teaches methods wherein a particular microsatellite status of a colorectal cancer tumor is determined based on higher or lower levels of particular polynucleotides disclosed in Table 17 and methods wherein downregulation of MLH1 polynucleotides in colorectal tumor samples is indicative of patients with sporadic disease and downregulation of PIWIL1 polynucleotides in colorectal tumor samples is indicative of patients with hereditary cases (pages 67-69, in particular). Such teachings demonstrate that the method does not function as claimed because downregulation of PIWIL1 polynucleotides in colorectal tumor samples is not indicative of patients with sporadic disease, as encompassed by the claims.

The level of unpredictability for using the presence or particular expression pattern of a particular molecule (or molecules) to detect any disease state is quite high. The state of the prior art dictates that one of skill in the art would not predict that a particular expression pattern of a particular molecule is indicative of a particular diseased state without a demonstration that said particular diseased stated correlates with said particular expression pattern of said particular molecule. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Prior to the successful application of newly described prognostic markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence demonstrating a particular expression pattern of particular molecules correlating with a particular diseased state, one of skill in the art would not predict said particular expression pattern of said particular molecules correlates with said particular diseased state without undue experimentation. Experimentation to identify such a correlation would in itself be inventive.

It is further noted that evidence abounds in which protein levels do not correlate with alterations in mRNA levels. There are many steps in the pathway leading from DNA to protein, and all of them can, in principle, be regulated. For example, Alberts *et al.* (Molecular Biology of the Cell, 3rd edition, 1994, page 465) illustrate post-transcriptional regulation of ferritin wherein the translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is

available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Further, Greenbaum *et al.* (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Thus, due to the multitude of homeostatic

factors affecting transcription and translation, protein levels do not predictably correlate with levels of mRNA (and vice-versa).

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods wherein just any microsatellite status of just any type of tumor from a cancer patient and just any prognostic marker determined from the amount or presence of just any plurality of gene expression products in just any sample from the cancer patient is indicative of just any classification of cancer, and Applicant has not enabled said methods because it has not been shown that just any microsatellite status of just any type of tumor from a cancer patient and just any prognostic marker determined from the amount or presence of just any plurality of gene expression products in just any sample from the cancer patient is indicative of just any classification of cancer.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Claim 94 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of classifying colorectal cancer patients with Dukes' B tumors wherein patients identified with microsatellite stable tumors exhibit poorer survival as compared to colorectal cancer patients with Dukes' B tumors with microsatellite instable tumors (pages 86-87), **the specification does not reasonably**

provide enablement for methods for classifying just any cancer in an individual comprising obtaining microsatellite status of said cancer wherein just any result is indicative of just any classification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to methods for classifying just any cancer in an individual comprising obtaining microsatellite status of said cancer wherein just any result is indicative of just any classification. This includes contradictory methods wherein a particular result is indicative of both a good classification and a bad classification.

This invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology". Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The specification teaches a method of classifying colorectal cancer patients with Dukes' B tumors wherein patients identified with microsatellite stable tumors exhibit

poorer survival as compared to colorectal cancer patients with Dukes' B tumors with microsatellite instable tumors (pages 86-87). Such teachings demonstrate that the method does not function as claimed because patients with Dukes' B tumors with microsatellite stable tumors do not exhibit *better* survival as compared to colorectal cancer patients with Dukes' B tumors with microsatellite instable tumors, as encompassed by the claims. It is further noted that the specification discloses microsatellite stability is not correlated with survival in patients with Dukes' C tumors receiving adjuvant chemotherapy.

The level of unpredictability for using a marker to detect any disease state is quite high. The state of the prior art dictates that one of skill in the art would not predict that a particular marker is indicative of a particular diseased state without a demonstration that said particular diseased stated correlates with said particular marker. In the instant case, the marker is microsatellite stability or microsatellite instability. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Prior to the successful application of newly described prognostic markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence demonstrating a particular marker correlating with a particular diseased state, one of skill in the art would not predict said particular marker correlates with said particular diseased state without undue experimentation. Experimentation to identify such a correlation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods for classifying just any cancer in an individual comprising obtaining microsatellite status of said cancer wherein just any result is indicative of just any classification, and Applicant has not enabled said methods because it has not been shown that just any result is indicative of just any classification of just any cancer.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Claim 95-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods wherein downregulation of MLH1 polynucleotides in colorectal tumor samples is indicative of patients with sporadic disease and downregulation of PIWIL1 polynucleotides in colorectal tumor samples is indicative of patients with hereditary cases (pages 67-69, in particular), **the specification does not reasonably provide enablement for** methods wherein just any classification of just any cancer is determined based on just any result obtained by a method comprising determining the expression of just any gene expression products forming a pattern that is indicative of the hereditary or sporadic nature of just any cancer in just any sample from a patient with just any cancer. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to methods wherein just any classification of just any cancer is determined based on just any result obtained by a method comprising determining the expression of just any gene expression products forming a pattern that is indicative of the hereditary or sporadic nature of just any cancer in just any sample from a patient with just any cancer.

This invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology". Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The specification teaches methods wherein downregulation of MLH1 polynucleotides in colorectal tumor samples is indicative of patients with sporadic disease and downregulation of PIWIL1 polynucleotides in colorectal tumor samples is indicative of patients with hereditary cases (pages 67-69, in particular). Such teachings demonstrate that the method does not function as claimed because downregulation of

PIWIL1 polynucleotides in colorectal tumor samples is not indicative of patients with *sporadic* disease, as encompassed by the claims.

The level of unpredictability for using the presence or particular expression pattern of a particular molecule (or molecules) to detect any disease state is quite high. The state of the prior art dictates that one of skill in the art would not predict that a particular expression pattern of a particular molecule is indicative of a particular diseased state without a demonstration that said particular diseased stated correlates with said particular expression pattern of said particular molecule. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Prior to the successful application of newly described prognostic markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence demonstrating a particular expression pattern of particular molecules correlating with a particular diseased state, one of skill in the art would not predict said particular expression pattern of said particular molecules correlates with said particular diseased state without undue experimentation. Experimentation to identify such a correlation would in itself be inventive.

It is further noted that evidence abounds in which protein levels do not correlate with alterations in mRNA levels. There are many steps in the pathway leading from DNA to protein, and all of them can, in principle, be regulated. For example, Alberts *et al.* (Molecular Biology of the Cell, 3rd edition, 1994, page 465) illustrate post-

transcriptional regulation of ferritin wherein the translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Further, Greenbaum *et al.* (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and

protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Thus, due to the multitude of homeostatic factors affecting transcription and translation, protein levels do not predictably correlate with levels of mRNA (and vice-versa).

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods wherein just any classification of just any cancer is determined based on just any result obtained by a method comprising determining the expression of just any gene expression products forming a pattern that is indicative of the hereditary or sporadic nature of just any cancer in just any sample from a patient with just any cancer, and Applicant has not enabled said methods because it has not been shown that just any result is indicative of just any classification of just any cancer.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Claims 69, 75, 82, 83, 95, 96, and 105 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of **a genus of gene expression products that form a pattern for**

sporadic or hereditary nature of just any cancer and **a genus of gene expression products that form a pattern for sporadic or hereditary nature of colon cancer**. However, the written description in this case only sets forth MLH1 polynucleotides and PIWIL1 polynucleotides as gene expression products that form a pattern for sporadic or hereditary nature of colon cancer. The specification does not disclose, and the art does not teach, the gene expression products that would and would not be encompassed by the genera.

The specification discloses downregulation of MLH1 polynucleotides in colorectal tumor samples is indicative of patients with sporadic disease and downregulation of PIWIL1 polynucleotides in colorectal tumor samples is indicative of patients with hereditary cases (pages 67-69, in particular). A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The inventions at issue in Lilly were DNA constructs per se, the holdings of that case is also applicable to claims such as those at issue here. Further, disclosure that

does not adequately describe a product itself logically cannot adequately describe a method of detecting that product.

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genera. That is, the specification provides neither a representative number of expression products that encompass the genera nor does it provide a description of structural features that are common to the genera. Since the disclosure fails to describe common attributes or characteristics that identify members of the genera, and because the genera is highly variant, the disclosure is insufficient to describe the genera. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genera as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genera, and therefore conception is not achieved until reduction to

practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 106-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of examining the sporadic or hereditary nature of colon cancer comprising detecting levels of MLH1 polynucleotides and PIWIL1 polynucleotides in colorectal tumor samples wherein downregulation of MLH1 polynucleotides in colorectal tumor samples is indicative of patients with sporadic disease and downregulation of PIWIL1 polynucleotides in colorectal tumor samples is indicative of patients with hereditary cases (pages 67-69, in particular), **the specification does not reasonably provide enablement for** methods of examining the sporadic or hereditary nature of colon cancer comprising performing just any histological examination of just any type of sample from a subject or just any genotyping of just any type of sample from a subject. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are drawn to methods of examining the sporadic or hereditary nature of colon cancer comprising performing just any histological examination of just any type of sample from a subject or just any genotyping of just any type of sample from a subject. This includes methods wherein histological examination or genotyping looking at markers unrelated to the sporadic or heredity nature of colon cancer are performed.

This invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology". Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The specification discloses downregulation of MLH1 polynucleotides in colorectal tumor samples is indicative of patients with sporadic disease and downregulation of PIWIL1 polynucleotides in colorectal tumor samples is indicative of patients with hereditary cases (pages 67-69, in particular). The specification does not disclose and

the art does not teach just any histological examination of just any type of sample from a subject or just any genotyping of just any type of sample from a subject would indicate sporadic or hereditary nature of colon cancer.

The level of unpredictability for using a marker to detect any disease state is quite high. The state of the prior art dictates that one of skill in the art would not predict that a particular marker is indicative of a particular diseased state without a demonstration that said particular diseased stated correlates with said particular marker. In the instant case, the marker is microsatellite stability or microsatellite instability. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Prior to the successful application of newly described prognostic markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence demonstrating a particular marker correlating with a particular diseased state, one of skill in the art would not predict said particular marker correlates with said particular diseased state without undue experimentation. Experimentation to identify such a correlation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods of examining the sporadic or hereditary nature of colon cancer comprising performing just any histological examination of just any type of sample from a subject or just any genotyping of just any type of sample from a subject, and Applicant has not enabled said methods because it

has not been shown that just any histological examination of just any type of sample from a subject and just any genotyping of just any type of sample from a subject would classify a colon cancer as sporadic or hereditary in nature.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Primary Examiner, Art Unit 1642